CLAIMS:

1. A method for identifying and/or obtaining a modulator of a rhomboid polypeptide, which method comprises:

(a) contacting a rhomboid polypeptide and a substrate polypeptide in the presence of a test compound and one or more non-rhomboid proteases,

wherein said substrate polypeptide comprises a core domain which has a rhomboid cleavable TMD sequence linked to an upstream tag sequence, the core domain sequence not being susceptible to cleavage by the one or more non-rhomboid proteases, and;

(b) determining the presence or amount in said medium of a soluble polypeptide fragment comprising said tag sequence.

2. A method according to claim 1 wherein said Rhomboid polypeptide and said substrate polypeptide are co-expressed in a cell.

3. A method according to claim 2 wherein the cell is a mammalian cell.

4. A method according to any one of claims 1 to 3 wherein the presence of the soluble substrate polypeptide is determined by;

(a) contacting said medium with an specific binding member which binds to said tag sequence, and

(b) determining binding of soluble polypeptide fragment to said binding member.

5. A method according to claim 4 wherein said specific binding member is immobilised.

6. A method according to claim 5 wherein said specific binding member is an antibody.

7. A method according to claim 6 wherein said antibody is immobilised on the surface of microtitre plate.

8. A method according to any one of the preceding claims wherein the substrate polypeptide comprises an extracellular detectable label.

9. A method according to claim 8 wherein the label is secreted alkaline phosphatase.

10. A method according to claim 8 or claim 9 wherein the binding of said polypeptide fragment to said anti-tag antibody is detected by determining the amount of said label bound to the antibody.

11. A method according to claim 10 wherein the amount of said label is determined by contacting said label with a reporter molecule which produces a signal in the presence of said label, and measuring said signal.

12. A method according to claim 11 wherein the signal is light emission.

13. A method according to any one of the preceding claims wherein the tag sequence is positioned 10 amino acid residues or less upstream of said TMD in said core domain.

14. A method according to any one of the preceding claim wherein the tag sequence consists of 30 amino acids or less.

15. A method according to any one of the preceding claims wherein the tag sequence is $MRGS(H)_6$.

16. A method according any one of the preceding claims wherein the rhomboid cleavage TMD rhomboid comprises a lumenal portion which has the same conformation within the membrane as Spitz residues 140-144.

17. A method according to claim 16 wherein the rhomboid cleavable TMD has a lumenal portion which comprises or consists of Spitz residues 140-144 (IASGA).

18. A method according to claim 16 or claim 17 wherein the rhomboid cleavable TMD is a rhomboid ligand TMD.

19. A method according to claim 18 wherein the rhomboid cleavable TMD is the Spitz TMD.

20. A method according to any one of the preceding claims wherein the substrate polypeptide comprises a cytoplasmic domain, said domain comprising the cytoplasmic domain of TGFα.

21. A method according to any one of the preceding claims wherein the substrate polypeptide comprises a cytoplasmic domain, said domain comprising the cytoplasmic domain of thrombomodulin.

22. A method according to any one of the preceding claims wherein the Rhomboid polypeptide has a sequence shown in Table 1.

23. A method according to claim 22 wherein the Rhomboid polypeptide is selected from the group consisting of Drosophila Rhomboid 1, Drosophila Rhomboid 2, Drosophila Rhomboid 3, Drosophila Rhomboid 4, Human RHBDL-1, Human RHBDL-2 and Human RHBDL-3, E. coli glgG, B. subtilis ypqP, P. stuartii A55862 gene product, P. aeruginosa B83259 gene product, S. cervisiae YGR101w and S. cervisiae YPL246c.

24. A method according to any one of the preceding claims comprising identifying said test compound as a modulator of Rhomboid protease activity.

25. A method according to claim 24 comprising isolating said test compound.

26. A method according to claim 25 comprising synthesising and/or preparing said test compound.

27. A method according to claim 25 or claim 26 comprising modifying said compound to optimise the pharmaceutical properties thereof.

28. A method according to any one of claims 24 to 27 comprising formulating said test compound in a pharmaceutical composition with a pharmaceutically acceptable excipient, vehicle or carrier.

29. A modulator of Rhomboid protease activity obtained by a method of any one of claims 1 to 23.

30. A method of making a pharmaceutical composition comprising,

identifying a compound as a modulator of Rhomboid activity using according to any one of claims 1 to 23,

synthesising, preparing or isolating said compound and

admixing the compound with a pharmaceutically acceptable excipient, vehicle or carrier, and optionally other ingredients to formulate or produce said composition.

31. A method according to claim 30 comprising modifying said compound to optimise the pharmaceutical properties thereof.

32. A method according to claim 30 or claim 31 comprising determining the activity of a Rhomboid polypeptide in the presence of said composition.

33. A polypeptide which is proteolytically cleavable by a Rhomboid polypeptide, said polypeptide comprising an a core domain which has a rhomboid cleavable TMD sequence linked to an upstream tag sequence, the core domain sequence not being susceptible to cleavage by mammalian metalloproteases.

34. A polypeptide according to claim 33 wherein the tag sequence is positioned 10 amino acid residues or less upstream of said TMD in said core domain.

35. A polypeptide according to claim 33 or 34 wherein the tag sequence consists of 15 amino acids or less.

36. A polypeptide according to claim 35 wherein the tag sequence is $MRGS(H)_6$

37. A polypeptide according to any one of claims 33 to 36 wherein the rhomboid cleavage TMD rhomboid comprises a lumenal portion which has the same conformation within the membrane as Spitz residues 140-144.

38. A polypeptide according to claim 37 wherein the rhomboid cleavable TMD has a lumenal portion which comprises or consists of Spitz residues 140-144 (IASGA).

39. A polypeptide according to claim 37 or claim 38 wherein the rhomboid cleavable TMD is a rhomboid ligand TMD.

40. A polypeptide according to claim 39 wherein the rhomboid cleavable TMD is the Spitz TMD.

41. A polypeptide according to any one of claims 33 to 40 wherein the substrate polypeptide comprises an extracellular domain, said domain comprising a detectable label.

42. A polypeptide according to claim 41 wherein the label is secreted alkaline phosphatase.

43. A polypeptide according to any one of claims 33 to 42 wherein the substrate polypeptide comprises a cytoplasmic domain, said domain comprising the cytoplasmic domain of thrombomodulin.

44. An isolated nucleic acid encoding a chimeric polypeptide according to any one of claims 33 to 43.

45. An expression vector comprising a nucleic acid according to claim 44.

46. A host cell comprising an expression vector according to claim 45 or a chimeric polypeptide according to any one of claims 33 to 43.

47. A host cell according to claim 46 further comprising an expression vector comprising a nucleic acid encoding a rhomboid polypeptide.

48. A method for obtaining a cleavage product of a Rhomboid polypeptide, which method comprises:

(a) contacting a Rhomboid polypeptide and a substrate polypeptide and one or more non-rhomboid proteases,

wherein said substrate polypeptide comprises a core domain which has a rhomboid cleavable TMD sequence linked to an upstream tag sequence, the core domain sequence not being susceptible to cleavage by the one or more non-rhomboid proteases, and;

(b) contacting said medium with an antibody which binds to said tag sequence, and

(c) isolating/purifying soluble polypeptide fragment bound to said antibody.

49. A method according to claim 48 comprising sequencing the polypeptide fragment.